A. HARRIS
285292A

```
=> fil reg

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                        ENTRY    SESSION
FULL ESTIMATED COST                                      0.31       0.46

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TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Structure search limits have been increased.  See HELP SLIMIT
for details.

=> e cyp24 gene/cn

E1            1     CYP-PA4/CN
E2            1     CYP1AD (MUS MUSCULUS KIDNEY)/CN
E3            0 --> CYP24 GENE/CN
E4            1     CYP2G1 (MOUSE OLFACTORY)/CN
E5            1     CYPAC 7005/CN
E6            1     CYPAC 7010/CN
E7            1     CYPAC X 7005/CN
E8            1     CYPAC X 7156-1/CN
E9            1     CYPAM/CN
E10           1     CYPAN/CN
E11           1     CYPAN C/CN
E12           1     CYPAR 7/CN

=> e cyp24/cn

E1            1     CYP-PA4/CN
E2            1     CYP1AD (MUS MUSCULUS KIDNEY)/CN
E3            0 --> CYP24/CN
E4            1     CYP2G1 (MOUSE OLFACTORY)/CN
E5            1     CYPAC 7005/CN
E6            1     CYPAC 7010/CN
E7            1     CYPAC X 7005/CN
E8            1     CYPAC X 7156-1/CN
E9            1     CYPAM/CN
E10           1     CYPAN/CN
E11           1     CYPAN C/CN
E12           1     CYPAR 7/CN

=> s cyp24 or cyp 24

            0 CYP24
          101 CYP
```

```
             4 CYPS
           105 CYP
                 (CYP OR CYPS)
        145398 24
             3 CYP 24
                 (CYP(W)24)
L1           3 CYP24 OR CYP 24

=> d 1-3 ide can


L1   ANSWER 1 OF 3  REGISTRY  COPYRIGHT 2001 ACS
RN   171402-67-8  REGISTRY
CN   Oxygenase, 25-hydroxycholecalciferol 24-mono- (mouse clone CDMhyd-15
     gene Cyp-24) (9CI)  (CA INDEX NAME)
FS   PROTEIN SEQUENCE
MF   Unspecified
CI   MAN
SR   CA
LC   STN Files:   CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
               1 REFERENCES IN FILE CA (1967 TO DATE)
               1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE   1:  124:24692

L1   ANSWER 2 OF 3  REGISTRY  COPYRIGHT 2001 ACS
RN   171402-66-7  REGISTRY
CN   Oxygenase, 25-hydroxycholecalciferol 24-mono- (mouse clone CDMhyd-15
     gene Cyp-24 precursor) (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Cytochrome P 450 (mouse precursor)
CN   Oxygenase, 1,25-dihydroxycholecalciferol 24-mono- (mouse precursor)
CN   Vitamin D 24-hydroxylase (mouse precursor)
FS   PROTEIN SEQUENCE
MF   Unspecified
CI   MAN
SR   CA
LC   STN Files:   CA, CAPLUS, TOXLIT

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
               2 REFERENCES IN FILE CA (1967 TO DATE)
               2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE   1:  127:90924

REFERENCE   2:  124:24692

L1   ANSWER 3 OF 3  REGISTRY  COPYRIGHT 2001 ACS
RN   171152-67-3  REGISTRY
CN   DNA (mouse clone CDMhyd-15 gene Cyp-24 25-hydroxycholecalciferol
     24-monooxygenase cDNA plus flanks) (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
```

CN **Deoxyribonucleic acid (mouse clone CDMhyd-15 gene Cyp-24 25-hydroxycholecalciferol 24-monooxygenase messenger RNA-complementary plus 5'- and 3'-flanking region fragment)**
OTHER NAMES:
CN GenBank D49438
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR GenBank
LC STN Files: BIOSIS, CA, CAPLUS, GENBANK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:24692

=> fil genbank

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	16.75	17.21

FILE 'GENBANK' ENTERED AT 15:09:35 ON 25 JAN 2001

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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s cyp24 or cyp 24

18	CYP24
440	"CYP"
357307	"24"
1	CYP 24 ("CYP"(W)"24")
L2 19	CYP24 OR CYP 24

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	4.60	21.81

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TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

```
=> e "25-hydroxyvitamin d3"/cn

E1            1     25-HYDROXYVITAMIN D2 25-GLUCURONIDE METHYL ESTER/CN
E2            1     25-HYDROXYVITAMIN D2 3-ACETATE/CN
E3            1 --> 25-HYDROXYVITAMIN D3/CN
E4            1     25-HYDROXYVITAMIN D3 1-HYDROXYLASE/CN
E5            1     25-HYDROXYVITAMIN D3 1.ALPHA.-HYDROXYLASE/CN
E6            1     25-HYDROXYVITAMIN D3 1.ALPHA.-HYDROXYLASE (HUMAN KIDNEY)/CN
E7            1     25-HYDROXYVITAMIN D3 1.ALPHA.-HYDROXYLASE (HUMAN)/CN
E8            1     25-HYDROXYVITAMIN D3 1.ALPHA.-HYDROXYLASE (MOUSE KIDNEY)/CN
E9            1     25-HYDROXYVITAMIN D3 1.ALPHA.-HYDROXYLASE (SWINE CLONE
1AH54
                    )/CN
E10           1     25-HYDROXYVITAMIN D3 23-HYDROXYLASE/CN
E11           1     25-HYDROXYVITAMIN D3 24-HYDROXYLASE/CN
E12           1     25-HYDROXYVITAMIN D3 24-HYDROXYLASE (RAT CLONE PCC24-8)/CN

=> e

E13           1     25-HYDROXYVITAMIN D3 25-GLUCURONIDE/CN
E14           1     25-HYDROXYVITAMIN D3 25-SULFATE/CN
E15           1     25-HYDROXYVITAMIN D3 26,23-LACTONE/CN
E16           1     25-HYDROXYVITAMIN D3 26-HYDROXYLASE/CN
E17           1     25-HYDROXYVITAMIN D3 27-HYDROXYLASE/CN
E18           1     25-HYDROXYVITAMIN D3 27-MONOOXYGENASE/CN
E19           1     25-HYDROXYVITAMIN D3 3-O-GLUCOSIDE/CN
E20           1     25-HYDROXYVITAMIN D3 3-SULFATE/CN
E21           1     25-HYDROXYVITAMIN D3 3.BETA.-SULFATE/CN
E22           1     25-HYDROXYVITAMIN D3 GLUCURONOSYLTRANSFERASE/CN
E23           1     25-HYDROXYVITAMIN D3-(26-3H) 3.BETA.-(BROMOACETATE)/CN
E24           1     25-HYDROXYVITAMIN D3-1.ALPHA.-HYDROXYLASE (RAT)/CN

=> s e11-12

              1 "25-HYDROXYVITAMIN D3 24-HYDROXYLASE"/CN
              1 "25-HYDROXYVITAMIN D3 24-HYDROXYLASE (RAT CLONE PCC24-8)"/CN
L3            2 ("25-HYDROXYVITAMIN D3 24-HYDROXYLASE"/CN OR
"25-HYDROXYVITAMIN
                D3 24-HYDROXYLASE (RAT CLONE PCC24-8)"/CN)

=> e vitamin d 24 hydroxylase/cn

E1            1     VITAMIN D/CN
E2            1     VITAMIN D 1.ALPHA.-HYDROXYLASE (HUMAN
MITOCHONDRIA-ASSOCIATE
                    D REDUCED)/CN
E3            0 --> VITAMIN D 24 HYDROXYLASE/CN
```

```
E4            1      VITAMIN D 24-HYDROXYLASE (MOUSE PRECURSOR)/CN
E5            1      VITAMIN D 25-HYDROXYLASE/CN
E6            1      VITAMIN D RECEPTOR (CATTLE)/CN
E7            1      VITAMIN D RECEPTOR (CHICKEN ISOFORM A)/CN
E8            1      VITAMIN D RECEPTOR (CHICKEN ISOFORM B)/CN
E9            1      VITAMIN D RECEPTOR (CROCODYLUS NILOTICUS LIVER FRAGMENT)/CN
E10           1      VITAMIN D RECEPTOR (HUMAN 427-AMINO ACID ISOFORM)/CN
E11           1      VITAMIN D RECEPTOR (HUMAN 450-AMINO ACID ISOFORM)/CN
E12           1      VITAMIN D RECEPTOR (HUMAN 477-AMINO ACID ISOFORM)/CN

=> s e4

L4            1 "VITAMIN D 24-HYDROXYLASE (MOUSE PRECURSOR)"/CN

=> e vitamin d receptor/cn 5

E1            1      VITAMIN D 24-HYDROXYLASE (MOUSE PRECURSOR)/CN
E2            1      VITAMIN D 25-HYDROXYLASE/CN
E3            0 --> VITAMIN D RECEPTOR/CN
E4            1      VITAMIN D RECEPTOR (CATTLE)/CN
E5            1      VITAMIN D RECEPTOR (CHICKEN ISOFORM A)/CN

=> s vitamin d receptor ?/cn

L5           13 VITAMIN D RECEPTOR ?/CN

=> fil medl,caplus,biosis,embase,wpids,jicst

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      15.82      37.63

FILE 'MEDLINE' ENTERED AT 15:11:10 ON 25 JAN 2001

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FILE 'JICST-EPLUS' ENTERED AT 15:11:10 ON 25 JAN 2001
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=> s cyp24 or cyp 24 or 11 or 12 or 13 or 14 or 25 hydroxyvitamin d3 24
hydroxylase enzyme or vitamin d24 hydroxylase

L6           33 FILE MEDLINE
L7          393 FILE CAPLUS
```

L8 139 FILE BIOSIS
L9 44 FILE EMBASE

EXCEEDS MAXIMUM FIELD LENGTH, WILL BE SEARCHED AS '25-HYDROXYVITAMIN D3 24-HYDROXYLASE (RAT CLONE PCC24-/CN'
L10 1 FILE WPIDS
L11 7 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L12 617 CYP24 OR CYP 24 OR L1 OR L2 OR L3 OR L4 OR 25 HYDROXYVITAMIN D3
24 HYDROXYLASE ENZYME OR VITAMIN D24 HYDROXYLASE

=> s l12 and (l5 or vdr or vitamin d receptor)

L13 7 FILE MEDLINE
L14 65 FILE CAPLUS
L15 25 FILE BIOSIS
L16 11 FILE EMBASE
L17 1 FILE WPIDS
L18 1 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L19 110 L12 AND (L5 OR VDR OR VITAMIN D RECEPTOR)

=> s l19 and (cancer or breast cancer or tumour or tumor)

L20 1 FILE MEDLINE
L21 12 FILE CAPLUS
L22 1 FILE BIOSIS
L23 0 FILE EMBASE
L24 1 FILE WPIDS
L25 0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L26 15 L19 AND (CANCER OR BREAST CANCER OR TUMOUR OR TUMOR)

=> dup rem l26

PROCESSING COMPLETED FOR L26
L27 14 DUP REM L26 (1 DUPLICATE REMOVED)

=> d cbib abs 1-14

L27 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
2000:725793 Document No. 133:291918 **CYP24** gene amplification and its use as marker for presence or progression of or predisposition to **cancer**. Albertson, Donna G.; Pinkel, Daniel; Collins, Colin; Gray, Joe W.; Ystra, Bauke (Regents of the University of California, USA).
PCT Int. Appl. WO 2000060109 A1 20001012, 73 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US5972 20000306. PRIORITY: US 1999-285292 19990402.
AB This invention pertains to the discovery that an amplification of the

CYP24 gene or an increase in **CYP24** activity is a marker for the presence of, progression of, or predisposition to, a **cancer** (e.g., **breast cancer**). Using this information, this invention provides methods of detecting a predisposition to **cancer** in an animal. The methods involve (i) providing a biol. sample from an animal (e.g. a human patient); (ii) detecting the level of **CYP24** within the biol. sample; and (iii) comparing the level of **CYP24** with a level of **CYP24** in a control sample taken from a normal, **cancer**-free tissue where an increased level of **CYP24** in the biol. sample compared to the level of **CYP24** in the control sample indicates the presence of said **cancer** in said animal.

L27 ANSWER 2 OF 14 MEDLINE

2000259547 Document Number: 20259547. Natural metabolites of 1alpha,25-dihydroxyvitamin D(3) retain biologic activity mediated through the **vitamin D receptor**. Harant H; Spinner D; Reddy G S; Lindley I J. (Department of Inflammatory Diseases, Novartis Research Institute, Vienna, Austria.. Hanna.Harant@pharma.novartis.com) . JOURNAL OF CELLULAR BIOCHEMISTRY, (2000 Apr) 78 (1) 112-20. Journal code: HNF. ISSN: 0730-2312. Pub. country: United States. Language: English.

AB 1alpha,25-dihydroxyvitamin D(3) (1alpha,25(OH)(2)D(3)), the active metabolite of vitamin D, mediates many of its effects through the intranuclear **vitamin D receptor** (**VDR** , NR1I1), that belongs to the large superfamily of nuclear receptors. **Vitamin D receptor** can directly regulate gene expression by binding to vitamin D response elements (VDREs) located in promoter or enhancer regions of various genes. Although numerous synthetic analogs of 1alpha,25(OH)(2)D(3) have been analysed for **VDR** binding and transactivation of VDRE-driven gene expression, the biologic activity of many naturally occurring metabolites has not yet been analyzed in detail. We therefore studied the transactivation properties of 1alpha,24R, 25-trihydroxyvitamin D(3) (1alpha,24R,25(OH)(3)D(3)), 1alpha, 25-dihydroxy-3-epi-vitamin D(3) (1alpha,25(OH)(2)-3-epi-D(3)), 1alpha,23S,25-trihydroxyvitamin D(3) (1alpha,23S,25(OH)(3)D(3)), and 1alpha-hydroxy-23-carboxy-24,25,26,27-tetranorvitamin D(3) (1alpha(OH)-24,25,26,27-tetranor-23-COOH-D(3); calcitroic acid) using the human G-361 melanoma cell line. Cells were cotransfected with a **VDR** expression plasmid and luciferase reporter gene constructs driven by two copies of the VDRE of either the mouse osteopontin promoter or the 1alpha,25(OH)(2)D(3) 24-hydroxylase (**CYP24**) promoter. Treatment with 1alpha,25(OH)(2)D(3) or the metabolites 1alpha,24R,25(OH)(3)D(3), 1alpha,25(OH)(2)-3-epi-D(3), and 1alpha,23S,25(OH)(3)D(3) resulted in transactivation of both constructs in a time- and dose-dependent manner, and a postitive regulatory effect was observed even for calcitroic acid in the presence of overexpressed **VDR**. The metabolites that were active in the reporter gene assay also induced expression of **CYP24** mRNA in the human keratinocyte cell line HaCaT, although with less potency than the parent hormone. A ligand-binding assay based on nuclear extracts from COS-1 cells overexpressing human **VDR** demonstrated that the metabolites,

although active in the reporter gene assay, were much less effective in displacing [(3)H]-labeled 1alpha,25(OH)(2)D(3) from **VDR** than the parent hormone. Thus, we report that several natural metabolites of 1alpha,25(OH)(2)D(3) retain significant biologic activity mediated through **VDR** despite their apparent low affinity for **VDR**.

L27 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2001 ACS
1999:795994 Document No. 132:31744 Gene probes used for genetic profiling in healthcare screening and planning. Roberts, Gareth Wyn (Genostic Pharma Ltd., UK). PCT Int. Appl. WO 9964627 A2 19991216, 745 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB1780 19990604. PRIORITY: GB 1998-12099 19980606; GB 1998-13291 19980620; GB 1998-13611 19980624; GB 1998-13835 19980627; GB 1998-14110 19980701; GB 1998-14580 19980707; GB 1998-15438 19980716; GB 1998-15576 19980718; GB 1998-15574 19980718; GB 1998-16085 19980724; GB 1998-16086 19980724; GB 1998-16921 19980805; GB 1998-17097 19980807; GB 1998-17200 19980808; GB 1998-17632 19980814; GB 1998-17943 19980819.

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies which comprises of the identification of the core group of genes and their sequence variants required to provide a broad base of clin. prognostic information - "genostics". The "Genostic.RTM." profiling of patients and persons will radically enhance the ability of clinicians, healthcare professionals and other parties to plan and manage healthcare provision and the targeting of appropriate healthcare resources to those deemed most

in need. The use of this invention could also lead to a host of new applications for such profiling technologies, such as identification of persons with particular work or environment related risk, selection of applicants for employment, training or specific opportunities or for the enhancing of the planning and organization of health services, education services and social services.

L27 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2001 ACS
1999:795993 Document No. 132:31743 Gene probes used for genetic profiling in
healthcare screening and planning. Roberts, Gareth Wyn (Genostic Pharma Limited, UK). PCT Int. Appl. WO 9964626 A2 19991216, 149 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB1779 19990604. PRIORITY: GB 1998-12098 19980606; GB 1998-28289 19981223.

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating
that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response.
In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol.
states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified
in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies.

L27 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2001 ACS
1999:270435 Document No. 131:53709 Liarozole acts synergistically with 1.alpha.,25-dihydroxyvitamin D3 to inhibit growth of DU 145 human prostate
cancer cells by blocking 24-hydroxylase activity. Ly, Lan H.; Zhao, Xiao-Yan; Holloway, Leah; Feldman, David (Department of Medicine, Division of Endocrinology, Stanford University School of Medicine, Stanford, CA, 94305, USA). Endocrinology, 140(5), 2071-2076 (English) 1999. CODEN: ENDOAO. ISSN: 0013-7227. Publisher: Endocrine Society.

AB 1.alpha.,25-Dihydroxyvitamin D3 [1,25-(OH)2D3] inhibits the proliferation of many **cancer** cells in culture, but not the aggressive human prostate **cancer** cell line DU 145. We postulated that the 1,25-(OH)2D3-resistant phenotype in DU 145 cells might result from the

high levels of expression of 25-hydroxyvitamin D-24-hydroxylase (24-hydroxylase) induced by treatment with 1,25-(OH)2D3. As this P 450 enzyme initiates 1,25-(OH)2D3 catabolism, we presumed that a high level of enzyme induction could limit the effectiveness of the 1,25-(OH)2D3 antiproliferative action. To examine this hypothesis we explored combination therapy with liarozole fumarate (R85,246), an imidazole deriv. currently in trials for prostate **cancer** therapy. As imidizole derivs. are known to inhibit P 450 enzymes, we postulated that this drug would inhibit 24-hydroxylase activity, increasing the 1,25-(OH)2D3 half-life, thereby enhancing 1,25-(OH)2D3 antiproliferative effects on DU 145 cells. Cell growth was assessed by measurement of viable cells using the MTS assay. When used alone, neither 1,25-(OH)2D3 (1-10 nm) nor liarozole (1-10 .mu.M) inhibited DU 145 cell growth. However, when added together, 1,25-(OH)2D3 (10 nM)/liarozole (1 .mu.M) inhibited growth 65% after 4 days of culture. We used a TLC method to assess 24-hydroxylase activity and demonstrated that liarozole (1-100 .mu.M) inhibited this P 450 enzyme in a dose-dependent manner. Moreover, liarozole treatment caused a significant increase in 1,25-(OH)2D3 half-life from 11 to 31 h. In addn., 1,25-(OH)2D3 can cause homologous up-regulation of the **vitamin D receptor** (**VDR**), and in the presence of liarozole, this effect was amplified, thus enhancing 1,25-(OH)2D3 activity. Western blot analyses demonstrated that DU 145 cells treated with 1,25-(OH)2D3/liarozole showed greater **VDR** up-regulation than cells treated with either drug alone. In summary, our data demonstrate that liarozole augments the ability of 1,25-(OH)2D3 to inhibit DU 145 cell growth. The mechanism appears to be due to inhibition of 24-hydroxylase activity, leading to increased 1,25-(OH)2D3 half-life and augmentation of homologous up-regulation of **VDR**. We raise the possibility that combination therapy using 1,25-(OH)2D3 and liarozole or other inhibitors of 24-hydroxylase, both in nontoxic doses, might serve as an effective treatment for prostate **cancer**.

L27 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2001 ACS
1998:54870 Document No. 128:162960 A highly sensitive method for large-scale measurements of 1,25-dihydroxyvitamin D. Arbour, Nancy C.; Ross, Troy K.; Zierold, Claudia; Prahl, Jean M.; Deluca, Hector F. (Department of Biochemistry, University of Wisconsin-Madison, Madison, WI, 53706, USA). Anal. Biochem., 255(1), 148-154 (English) 1998. CODEN: ANBCA2. ISSN: 0003-2697. Publisher: Academic Press.

AB A quant. method for measuring 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3) was developed utilizing a luciferase reporter gene under the control of the highly inducible 25-hydroxyvitamin D3 24-hydroxylase promoter in a stably transfected cell line. Transient transfections with constructs contg. the 24-hydroxylase gene promoter 5' to a luciferase reporter were first performed in cell lines with high levels of **vitamin D receptor**, i.e., the rat osteosarcoma (ROS 17/2.8) and human **breast cancer** (T-47D) cell lines. ROS 17/2.8 cells, stably transfected with the plasmid, gave a 60-fold stimulation with

M 1,25-(OH)2D3. A std. curve was constructed showing a large range of response to 1,25-(OH)2D3 (1 pg to 1 ng). The assay was adapted to microtiter plates, which permits a large no. of samples to be assayed simultaneously. Other metabolites of vitamin D and analogs such as 25-hydroxyvitamin D3, 24,25-dihydroxyvitamin D3, and 1.alpha.-hydroxyvitamin D3 have negligible effects on the detection of 1,25-(OH)2D3, thus eliminating the need for purifn. of sample. The sensitivity of the method permitted the use of 100 .mu.l of serum with excellent results. Comparison of this method with a com. available assay demonstrates that it gives higher sensitivity, simpler manipulations, and comparable results.

L27 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2001 ACS
1996:691420 Document No. 126:43054 Developmental expression of calcitriol receptors, 9-kilodalton calcium-binding protein, and calcidiol 24-hydroxylase in human intestine. Delvin, Edgard E.; Lopez, Valerie; Levy, Emile; Menard, Daniel (Hopital Ste-Justine, Centre de recherche, Montreal, PQ, Can.). Pediatr. Res., 40(5), 664-670 (English) 1996. CODEN: PEREBL. ISSN: 0031-3998. Publisher: Williams & Wilkins.

AB Human intestinal mucosa consists of highly active epithelial cells in continual renewal and differentiation processes located at different portions of the villi. The crypt contains abundant replicating cells which, upon reaching the villus tip, acquire their fully differentiated state. Besides its well recognized role in bone cell homeostasis, calcitriol has been attributed a role in cellular differentiation and proliferation in normal leukocytes and myeloid leukemia cells. We have previously documented the presence and the distribution of specific calcitriol receptors in the cells of the small and large intestine from 13-20-wk-old human fetuses and that calcitriol was able to promote human intestinal epithelium proliferation or differentiation, in organ culture, depending upon fetal age. We now show that, whereas transcripts for calcitriol receptors are abundant from duodenum to colon, those for the 9 kDa calcium-binding protein are present mainly in the duodenum and the jejunum and to a lesser extent in the ileum and the colon. Transcripts for 25-hydroxycholecalciferol-24-hydroxylase could not be detected in any of the intestine segments despite a prolonged exposition of the gels. Immunofluorescence staining for the 9 kDa calcium-binding protein was exclusively obsd. in the epithelial cells of the small intestine and colon, the subepithelial layers being always neg. The 9 kDa calcium-binding protein distribution along the crypt-villus axis appeared as a gradient, increasing from the developing crypt to the tip of the villus in the duodenum, jejunum, and ileum. Based on the present observations and on the fact that calcitriol promotes human fetal proliferation and differentiation, the presence of transcripts for calcitriol receptors and 9 kDa calcium-binding protein in the intestinal cell opens interesting possibilities as of their role in the in utero human gut development and the control of colorectal **cancers**.

L27 ANSWER 8 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
1996:511228 Document No.: PREV199699233584. **Vitamin D receptor** expression is required for growth modulation by 1-alpha,25-dihydroxyvitamin D-3 in the human prostatic carcinoma cell line

ALVA-31. Hedlund, T. E.; Moffatt, K. A.; Miller, G. J. (1). (1) Dep. Pathol., Box B-216, Univ. Colorado Health Sci. Cent., 4200 E. Ninth Ave., Denver, CO 80262 USA. Journal of Steroid Biochemistry and Molecular

Biology, (1996) Vol. 58, No. 3, pp. 277-288. ISSN: 0960-0760. Language: English.

AB Epidemiological data suggest that vitamin D-3, obtained from dietary sources and sunlight exposure, protects against mortality from prostate **cancer** (PC). In agreement with this, the most active vitamin D metabolite 1-alpha,25-dihydroxyvitamin D-3 (1,25(OH)-2D-3) regulates the growth and differentiation of several human PC cell lines. Both genomic and non-genomic signalling pathways for 1,25(OH)-2 D-3 have been reported, although the mechanism of action in PC cells has not been defined. We now provide data supporting an active role for the nuclear **vitamin D receptor** (**VDR**) in mediating the growth-inhibitory effects of 1,25(OH)-2 D-3 on these cells. In the **VDR**-rich cell line ALVA-31, the observed changes in growth by 1,25(OH)-2 D-3 are preceded by significant changes in **VDR** mRNA expression. In contrast, the cell line JCA-1, containing few **VDRs**, fails to show both early changes in **VDR** gene expression and later changes in growth with 1,25(OH)-2 D-3. To assess the role of the **VDR** more directly, transfection studies were pursued. ALVA-31 cells were stably transfected with an antisense **VDR** cDNA construct in an attempt to reduce **VDR** expression. Antisense mRNA expression among clones was associated with: (a) reduced or abolished sensitivity to the effects of 1,25(OH)-2D-3, on growth; (b) decreased numbers of **VDRs** per cell, as measured by radiolabelled-ligand binding; and (c) a lack of induction of the **VDR**-regulated enzyme 24-hydroxylase in response to 1,25(OH)-2D-3. From these studies we conclude that the antiproliferative effects of 1,25(OH), D, require expression of the nuclear **VDR** in this system.

L27 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2001 ACS

1996:93022 Document No. 124:199250 Simian virus 40-, but not human papillomavirus-, transformation of prostatic epithelial cells results in loss of growth-inhibition by 1,25-dihydroxyvitamin D3. Gross, Coleman; Skowronski, Roman J.; Plymate, Stephen R.; Rhim, Johng S.; Peehl, Donna M.; Feldman, David (School Medicine, Stanford University, Stanford, CA, 94305, USA). Int. J. Oncol., 8(1), 41-7 (English) 1996. CODEN: IJONES. ISSN: 1019-6439.

AB In addn. to its well-known calcemic actions, 1,25-dihydroxyvitamin D3 [1,25(OH)2D] exhibits differentiating and antiproliferative effects in several types of **cancer** cells. 1,25(OH)2D receptors (**VDR**) as well as 1,25(OH)2D-mediated growth-inhibition have been demonstrated in human prostate **cancer** cell lines. To further develop model systems for the study of 1,25(OH)2D action and to elucidate the mechanism of growth-inhibition, the authors studied several human prostate cell lines immortalized with either simian virus 40 (SV40) or human papillomavirus type 18 (HPV). The SV40-transformed cell lines P69S40-T and P153SV40-T were not growth-inhibited by 1,25(OH)2D at concns. as high as 100 nM, whereas the HPV-transformed cells PZ-HPV-7 and CA-HPV-10 were growth-inhibited. All cell lines expressed **VDR**, and **VDR** mRNA was demonstrated by Northern blot anal. All cells exhibited induction of 24-hydroxylase mRNA, a 1,25(OH)2D-responsive gene, after 1,25(OH)2D treatment. To understand the apparent dissocn. of 1,25(OH)2D actions in the SV40-transformed cells, the authors turned to the human prostate **cancer** cell line DU 145. These cells, like the SV40-transformed cells, are not growth-inhibited but demonstrate

induction of 24-hydroxylase mRNA after 1,25(OH)2D treatment. DU 145 cells
contain a mutated retinoblastoma gene (Rb) which contributes to their uncontrolled growth, analogous to the disruption of Rb by SV40 and HPV. The authors compared DU 145 cells to DU 145 cells transfected with normal Rb (DU 145/Rb). Similar to DU 145, DU 145/Rb cells were not growth-inhibited by 1,25(OH)2D, while 24-hydroxylase mRNA was induced. These results suggest that divergent pathways mediate the growth-inhibitory effect of 1,25(OH)2D and its induction of 24-hydroxylase. It also appears that the antiproliferative effect of 1,25(OH)2D is mediated by an Rb-independent mechanism.

L27 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2001 ACS
1995:722875 Document No. 123:133059 Development of a biologically active fluorescent-labeled calcitriol and its use to study hormone binding to the
vitamin D receptor. Barsony, Julia; Renyi, Istvan; McKoy, Wilma; Kang, Hee Chol; Haugland, Richard P.; Smith, Catharine L. (Metabolic Diseases Branch, Natl. Inst. Diabetes, Digestive, and Kidney Diseases, Bethesda, MD, 20892-0850, USA). Anal. Biochem., 229(1), 68-79 (English) 1995. CODEN: ANBCA2. ISSN: 0003-2697.
AB To gain better insight into the mechanism of steroid receptor activation and calcitriol actions, the authors have developed the first pharmacol. relevant fluorescent-labeled ligand for the **vitamin D receptor** (**VDR**). Purity and structure of three borondipyrromethene difluoride (BODIPY)-labeled calcitriol derivs. were characterized by TLC, HPLC, and 1H-NMR spectroscopy. 3.beta.-BODIPY-calcitriol was the most potent deriv. to induce 25-hydroxyvitamin D3 24-hydroxylase activity and to inhibit cell proliferation. It was taken up rapidly and specifically and was not cleaved by endogenous esterases. 3.beta.-BODIPY-calcitriol also retained high-affinity binding to the **VDR**. Hormone binding to the receptor was measured by spectrofluorometry in high-salt exts. from cultured cells with wild-type **VDR**, from cells virally overexpressing the human **VDR**, and in intact cells with and without **VDR**. Results from fluorescent binding studies agreed with results from radioligand assays. The most useful feature of this reagent is that its fluorescence emission increases severalfold upon binding to **VDR**. This allows direct monitoring by microscopy of ligand receptor interactions in living cells. Fluorescent-labeled calcitriol can be a valuable diagnostic tool for **cancer** research and is essential for exploring the subcellular localization of **VDRs**.

L27 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2001 ACS
1995:326434 Document No. 122:96002 Actions of vitamin D3 analogs on human prostate **cancer** cell lines: comparison with 1,25-dihydroxyvitamin D3. Skowronski, Roman J.; Peehl, Donna M.; Feldman, David (Dep. Med. and Urology (D.M.P.), Stanford Univ. Sch. Med., Stanford, CA, 94305, USA). Endocrinology, 136(1), 20-6 (English) 1995. CODEN: ENDOAO. ISSN: 0013-7227.
AB Data from epidemiol. studies has suggested that vitamin D deficiency may promote prostate **cancer**, although the mechanism is not understood. The authors have previously demonstrated the presence of **vitamin D receptors** (**VDR**) in three human prostate carcinoma cell lines (LNCaP, PC-3, and DU-145) as well as

in primary cultures of stromal and epithelial cells derived from normal and malignant prostate tissues. The authors have also shown that 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3] can elicit an antiproliferative action in these cells. In the present study the authors compared the biol. actions of 1,25-(OH)2D3 to those of a series of natural vitamin D3 metabolites and several synthetic analogs of vitamin D3 known to exhibit less hypercalcemic activity in vivo. In ligand binding competition expts., the authors demonstrated the following order of potency in displacing [3H]1,25-(OH)2D3 from **VDR**: EB-1089 > 1,25-(OH)2D3 > MC-903 > 1,24,25(OH)3D3 > 22-oxacalcitriol (OCT) > 1.alpha.,25-dihydroxy-16-ene-cholecalciferol (Ro 24-2637) > 25-hydroxyvitamin D3, with EB-1089 being .apprx.2-fold more potent than the native hormone. No competitive activity was found for 25-hydroxy-16,23-diene-cholecalciferol. When compared for ability to inhibit proliferation of LNCaP cells, MC-903, EB-1089, OCT, and Ro 24-2637 exhibited 4-, 3-, 3-, and 2-fold greater inhibitory activity than 1,25-(OH)2D3. Interestingly, although OCT and Ro 24-2637 exhibit, resp., 10 and 14 times lower affinity for **VDR** than 1,25-(OH)2D3, both compds. inhibited the proliferation of LNCaP cells with a potency greater than that of the native hormone. The relative potency of vitamin D3 metabolites and analogs to inhibit cell proliferation correlated well with the ability of these compds. to stimulate prostate-specific antigen secretion by LNCaP cells as well as with their potency to induce the 25-hydroxyvitamin D3-24-hydroxylase mRNA transcript in PC-3 cells. In conclusion, these results demonstrate that synthetic analogs of vitamin D3, known to exhibit reduced calcemic activity, can elicit antiproliferative effects and other biol. actions in LNCaP and PC-3 cell lines. It is noteworthy that although binding to **VDR** is crit. for 1,25-(OH)2D3 action, the analog data indicate that addnl. factors significantly contribute to the magnitude of the biol. response. Finally, the strong antiproliferative effects of several synthetic analogs known to exhibit less calcemic activity than 1,25-(OH)2D3 suggest that these compds. potentially may be useful as an addnl. therapeutic option for the treatment of prostate **cancer**.

L27 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2001 ACS

1995:706195 Document No. 123:161606 Actions of 1,25-dihydroxyvitamin D and synthetic analogs on cultured human prostate carcinoma cells. Skowronski, Roman J.; Peehl, Donna M.; Cramer, Scott; Feldman, David (School Medicine, Stanford University, Stanford, CA, 94305, USA). Proc. Workshop Vitam. D, 9th(Vitamin D), 520-1 (English) 1994. CODEN: PWVDDU. ISSN: 0721-7110.

AB It is shown that benign and malignant human prostate carcinoma cells possess **VDR** and that 1,25-dihydroxyvitamin D treatment can elicit an antiproliferative action in these cells. Although binding to **VDR** is crit. for 1,25-dihydroxyvitamin D action, analog data indicates that addnl. factors contribute to detg. the magnitude of the biol. response. The strong antiproliferative effects of several synthetic analogs known to exhibit less calcemic activity than 1,25-dihydroxyvitamin D, may indicate their pot. use as an addnl. therapeutic option for treatment of prostate **cancer**.

L27 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2001 ACS
1995:706194 Document No. 123:282214 Biologically active receptors for vitamin D3 are present in multiple human prostatic carcinoma cell lines. Miller, Gary J.; Hedlund, Tammy E.; Moffatt, Kirsten A. (Health Sciences Center, University Colorado, Denver, CO, 80262, USA). Proc. Workshop Vitam. D, 9th(Vitamin D), 514-15 (English) 1994. CODEN: PWVDDU. ISSN: 0721-7110.

AB Seven prostatic carcinoma cell lines (ALVA-31,. PPC-1, TSU-Pr1, JCA-1, PC-3, DU145, and LNCaP) were examd. for biol. active vitamin D3 receptors (**VDr**). The results suggest that the presence of biol. active **VDr** is a ubiquitous feature of prostatic carcinoma cell lines. Both growth and expression of 25-(OH)-D3-24 hydroxylase activity was modulated by incubation with 1.alpha.,25-(OH)2-D3 in vitro. Thus, 1.alpha.,25-(OH)2-D3 might act in vivo to promote the differentiation and slow the progression of prostatic **cancer** in patients.

L27 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2001 ACS
1993:252429 Document No. 118:252429 Regulation of **vitamin D receptor** abundance and responsiveness during differentiation of HT-29 human colon **cancer** cells. Zhao, Xi; Feldman, David (Sch. Med., Stanford Univ., Stanford, CA, 94305, USA). Endocrinology (Baltimore), 132(4), 1808-14 (English) 1993. CODEN: ENDOAO. ISSN: 0013-7227.

AB We have studied the effects of 1,25-dihydroxyvitamin D [1,25-(OH)2D3] on cellular differentiation in the HT-29 human colon **cancer** cell line. Our aim was to evaluate the regulation of 1,25-dihydroxyvitamin D receptor (**VDR**) abundance and hormone responsiveness during the transition of rapidly proliferating to differentiated cells. Differentiation was induced by three means: cells were cultured in galactose-supplemented medium without glucose (GAL), grown on Matrigel-coated surfaces (MTG), or treated with 1,25(OH)2D3. Cell proliferation, assessed by [3H]thymidine incorporation, was equivalently inhibited by treatment with 1,25(OH)2D3, GAL or MTG. Differentiation was assessed by the induction of amino-oligo peptidase activity which was low in the proliferating cells. Following treatment with 1,25(OH)2D3, or growth in GAL or on MTG, amino-oligo peptidase activity increased 8- to 9-fold. The abundance of **VDR** measured by [3H]1,25(OH)2D3 binding, decreased to half without significant change in affinity, in cells differentiated by all three means compared to proliferating cells. Northern blot analyses of differentiated cells showed decreased steady-state levels of **VDR** mRNA (mRNA), indicating that all three treatments wimilarly decreased the abundance of **VDR**, at least in part, at the mRNA level. When exposed to 1,25(OH)2D3, the proliferating cells exhibited homologous up-regulation of **VDR** as well as the induction of 24-hydroxylase mRNA; the differentiated cell failed to exhibit both of these biol. responses. Our findings demonstrate that 1,25(OH)2D3, GAL and MTG treatment all inhibit HT-29 cell proliferation and stimulate differentiation. Postproliferative differentiation achieved by the three approaches was assocd. with decreased **VDR** abundance, loss of **VDR** homologous up-regulation, and development of hormone unresponsiveness to 1,25(OH)2D3.

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TOTAL FOR ALL FILES
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L63 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
2000:790675 Document No. 133:330496 Comparative fluorescence hybridization to oligonucleotide microarrays used for precise mapping of chromosomal abnormalities assocd. with disease. **Gray, Joe W.**; Pinkel, Dan; Albertson, Donna G.; Collins, Colin C.; Baldocchi, Russell A. (The Regents of the University of California, USA). PCT Int. Appl. WO 2000066779 A1 20001109, 28 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US11433 20000428. PRIORITY: US 1999-302056 19990429.

AB The present invention provides methods of detg. relative copy no. of target nucleic acid sequences and precise mapping of chromosomal abnormalities assocd. with disease. The methods of the invention use target nucleic acid sequences immobilized on a solid surface, to which a sample comprising two sets of differentially labeled nucleic acid sequences are hybridized. The hybridization of the labeled nucleic acid sequences to the solid surface is then detected using std. techniques.

L63 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 2
2000:725793 Document No. 133:291918 CYP24 gene amplification and its use as marker for presence or progression of or predisposition to cancer. **Albertson, Donna G.**; Pinkel, Daniel; Collins, Colin; Gray, Joe W.; Ystra, Bauke (Regents of the University of California, USA). PCT Int. Appl. WO 2000060109 A1 20001012, 73 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US5972 20000306. PRIORITY: US 1999-285292 19990402.

AB This invention pertains to the discovery that an amplification of the CYP24 gene or an increase in CYP24 activity is a marker for the presence of, progression of, or predisposition to, a cancer (e.g., breast cancer). Using this information, this invention provides methods of detecting a predisposition to cancer in an animal. The methods involve (i) providing a biol. sample from an animal (e.g. a human patient); (ii) detecting the level of CYP24 within the biol. sample; and (iii) comparing the level of CYP24 with a level of CYP24 in a control sample taken from a normal, cancer-free tissue where an increased level of CYP24 in the biol. sample

compared to the level of CYP24 in the control sample indicates the presence of said cancer in said animal.

L63 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 3
2000:133894 Document No. 132:162022 Novel amplicon in the 20q13 region of human chromosome 20 and uses thereof. **Albertson, Donna**; Pinkel, Daniel; Collins, Colin; Gray, Joe (The Regents of the University of California, USA). PCT Int. Appl. WO 2000009758 A1 20000224, 48 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US18483 19990812. PRIORITY: US 1998-134044 19980814.
AB The invention presents a method (comparative genomic hybridization) for screening human chromosome 20q13.2 genomic DNA for the presence of an amplicon. The invention relates that sequences from the amplicon can be used as a probe to det. the copy no. of the amplicon in a DNA sample. Detn. of copy no. can be used in the diagnosis or prognosis of cancer, esp. breast cancer. The invention also relates that the probe can hybridize specifically to sequences spanning the distance between D20S120 and D20S211 on chromosome 20, which contains a no. of cloned sequences, STS markers, and GDB loci. The invention further relates that the probe can comprise a polymerase chain reaction (PCR) primer pair able to amplify some or all of the sequences from D20S120 and D20S211. The invention also provides a diagnostic kit for detection of alteration in amplicon copy no. which contains a probe specific for the amplicon and a blocking nucleic acid (Cot-1 DNA).

L63 ANSWER 4 OF 9 BIOSIS COPYRIGHT 2001 BIOSIS
2000:275352 Document No.: PREV200000275352. Oligonucleotide-array-based comparative genomic hybridization. Baldocchi, Russ A. (1); Glynne, Richard J.; Kowbel, Dave; Tom, Ed; Segraves, Rick; **Albertson, Donna**; **Pinkel, Dan**; **Collins, Colin**; Mack, David H.; **Gray, Joe W.**. (1) Eos Biotech, Inc, S.San Francisco, CA USA. Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 724. print.. Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000 ISSN: 0197-016X. Language: English. Summary Language: English.

L63 ANSWER 5 OF 9 MEDLINE DUPLICATE 4
2000296614 Document Number: 20296614. Quantitative mapping of amplicon structure by array CGH identifies CYP24 as a candidate oncogene. **Albertson D G**; Ylstra B; Segraves R; **Collins C**; Dairkee S H; Kowbel D; Kuo W L; **Gray J W**; **Pinkel D**. ([1] Cancer Research Institute, University of California, San Francisco, Box 0808, San Francisco, California, USA.. albertson@cc.ucsf.edu) . NATURE GENETICS, (2000 Jun) 25 (2) 144-6. Journal code: BRO. ISSN: 1061-4036. Pub. country: United States. Language: English.
AB We show here that quantitative measurement of DNA copy number across amplified regions using array comparative genomic hybridization (CGH) may facilitate oncogene identification by providing precise information on the

locations of both amplicon boundaries and amplification maxima. Using this analytical capability, we resolved two regions of amplification within an approximately 2-Mb region of recurrent aberration at 20q13.2 in breast cancer. The putative oncogene ZNF217 (ref. 5) mapped to one peak, and CYP24 (encoding vitamin D 24 hydroxylase), whose overexpression is likely to lead to abrogation of growth control mediated by vitamin D, mapped to the other.

L63 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 5
1998:492622 Document No. 129:229013 Positional cloning of ZNF217 and NABC1: genes amplified at 20q13.2 and overexpressed in breast carcinoma. **Collins, Colin**; Rommens, Johanna M.; Kowbel, David; Godfrey, Tony; Tanner, Minna; Hwang, Soo-In; Polikoff, Daniel; Nonet, Genevieve; Cochran, Joanne; Myambo, Ken; Jay, Karen E.; Froula, Jeff; Cloutier, Thomas; Kuo, Wen-Lin; Yaswen, Paul; Dairkee, Shanaz; Giovanola, Jennifer; Hutchinson, Gordon B.; Isola, Jorma; Kallioniemi, Olli-P.; Palazzolo, Mike; Martin, Chris; Ericsson, Cheryl; **Pinkel, Dan**; **Albertson, Donna**; Li, Wu-Bo; **Gray, Joe W.** (Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA, 94720, USA). Proc. Natl. Acad. Sci. U. S. A., 95(15), 8703-8708 (English) 1998. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.
AB The authors report here the mol. cloning of an .apprxeq.1-Mb region of recurrent amplification at 20q13.2 in breast cancer and other tumors and the delineation of a 260-kb common region of amplification. Anal. of the 1-Mb region produced evidence for five genes, ZNF217, ZNF218, and NABC1, PIC1L (PIC1-like), CYP24, and a pseudogene CRP (Cyclophillin Related Pseudogene). ZNF217 and NABC1 emerged as strong candidate oncogenes and were characterized in detail. NABC1 is predicted to encode a 585-aa protein of unknown function and is overexpressed in most but not all breast cancer cell lines in which it was amplified. ZNF217 is centrally located in the 260-kb common region of amplification, transcribed in multiple normal tissues, and overexpressed in all cell lines and tumors in which it is amplified and in two in which it is not. ZNF217 is predicted to encode alternately spliced, Kruppel-like transcription factors of 1,062 and 1,108 aa, each having a DNA-binding domain (eight C2H2 zinc fingers) and a proline-rich transcription activation domain.

L63 ANSWER 7 OF 9 BIOSIS COPYRIGHT 2001 BIOSIS
1998:196225 Document No.: PREV199800196225. Analysis of DNA sequence copy number variation in breast cancer using comparative genomic hybridization to DNA microarrays. **Albertson, D. G. (1)**; Segraves, R.; Sudar, D. (1); Clark, S.; **Collins, C. (1)**; Chen, C.; Kuo, W.-L.; Kowbel, D. (1); Dairkee, S. H.; Poole, I.; **Gray, J. W. (1)**; **Pinkel, D. (1)**. (1) E.O. Lawrence Berkeley National Lab., Berkeley, CA USA. Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1998) Vol. 39, pp. 345. Meeting Info.: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998 American Association for Cancer Research. ISSN: 0197-016X. Language: English.

L63 ANSWER 8 OF 9 MEDLINE DUPLICATE 6
1998442661 Document Number: 98442661. High resolution analysis of DNA copy

number variation using comparative genomic hybridization to microarrays. **Pinkel D**; Segraves R; Sudar D; Clark S; Poole I; Kowbel D; **Collins C**; Kuo W L; Chen C; Zhai Y; Dairkee S H; Ljung B M; **Gray J W**; **Albertson D G**. (Cancer Genetics Program, UCSF Cancer Center, University of California San Francisco, 94143-0808, USA.. pinkel@cc.usf.edu) . NATURE GENETICS, (1998 Oct) 20 (2) 207-11. Journal code: BRO. ISSN: 1061-4036. Pub. country: United States. Language: English.

AB Gene dosage variations occur in many diseases. In cancer, deletions and copy number increases contribute to alterations in the expression of tumour-suppressor genes and oncogenes, respectively. Developmental abnormalities, such as Down, Prader Willi, Angelman and Cri du Chat syndromes, result from gain or loss of one copy of a chromosome or chromosomal region. Thus, detection and mapping of copy number abnormalities provide an approach for associating aberrations with disease phenotype and for localizing critical genes. Comparative genomic hybridization (CGH) was developed for genome-wide analysis of DNA sequence copy number in a single experiment. In CGH, differentially labelled total genomic DNA from a 'test' and a 'reference' cell population are cohybridized to normal metaphase chromosomes, using blocking DNA to suppress signals from repetitive sequences. The resulting ratio of the fluorescence intensities at a location on the 'cytogenetic map', provided by the chromosomes, is approximately proportional to the ratio of the copy numbers of the corresponding DNA sequences in the test and reference genomes. CGH has been broadly applied to human and mouse malignancies. The use of metaphase chromosomes, however, limits detection of events involving small regions (of less than 20 Mb) of the genome, resolution of closely spaced aberrations and linking ratio changes to genomic/genetic markers. Therefore, more laborious locus-by-locus techniques have been required for higher resolution studies. Hybridization to an array of mapped sequences instead of metaphase chromosomes could overcome the limitations of conventional CGH (ref. 6) if adequate performance could be achieved. Copy number would be related to the test/reference fluorescence ratio on the array targets, and genomic resolution could be determined by the map distance between the targets, or by the length of the cloned DNA segments. We describe here our implementation of array CGH. We demonstrate its ability to measure copy number with high precision in the human genome, and to analyse clinical specimens by obtaining new information on chromosome 20 aberrations in breast cancer.

L63 ANSWER 9 OF 9 BIOSIS COPYRIGHT 2001 BIOSIS

1998:190153 Document No.: PREV199800190153. High resolution analysis of DNA copy number variation using comparative genomic hybridization to DNA microarrays. **Pinkel, D. (1)**; Segraves, R.; Sudar, D.; Poole, S. Clark I.; Jones, A.; **Collins, C.**; Zou, Y.; Dairkee, S.; **Gray, J.**; **Albertson, D. (1)**. (1) Univ. Calif. San Francisco, San Francisco, CA USA. Cytometry, (1998) No. SUPPL. 9, pp. 24-25. Meeting Info.: XIX International Congress of the International Society for Analytical Cytology Colorado Springs, Colorado, USA February 28-March 5, 1998 International Society for Analytical Cytology. ISSN: 0196-4763. Language: English.

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=> dis his

     (FILE 'HOME' ENTERED AT 15:08:30 ON 25 JAN 2001)

     FILE 'REGISTRY' ENTERED AT 15:08:42 ON 25 JAN 2001

     FILE 'REGISTRY' ENTERED AT 15:08:55 ON 25 JAN 2001
               E CYP24 GENE/CN
               E CYP24/CN
L1           3 S CYP24 OR CYP 24

     FILE 'GENBANK' ENTERED AT 15:09:35 ON 25 JAN 2001
L2          19 S CYP24 OR CYP 24

     FILE 'REGISTRY' ENTERED AT 15:09:49 ON 25 JAN 2001
               E "25-HYDROXYVITAMIN D3"/CN
L3           2 S E11-12
               E VITAMIN D 24 HYDROXYLASE/CN
L4           1 S E4
               E VITAMIN D RECEPTOR/CN 5
L5          13 S VITAMIN D RECEPTOR ?/CN

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, WPIDS, JICST-EPLUS' ENTERED AT
     15:11:10 ON 25 JAN 2001
L6          33 FILE MEDLINE
L7         393 FILE CAPLUS
L8         139 FILE BIOSIS
L9          44 FILE EMBASE
L10          1 FILE WPIDS
L11          7 FILE JICST-EPLUS
     TOTAL FOR ALL FILES
L12        617 S CYP24 OR CYP 24 OR L1 OR L2 OR L3 OR L4 OR 25
HYDROXYVITAMIN
L13          7 FILE MEDLINE
L14         65 FILE CAPLUS
L15         25 FILE BIOSIS
L16         11 FILE EMBASE
L17          1 FILE WPIDS
L18          1 FILE JICST-EPLUS
     TOTAL FOR ALL FILES
L19        110 S L12 AND (L5 OR VDR OR VITAMIN D RECEPTOR)
L20          1 FILE MEDLINE
L21         12 FILE CAPLUS
L22          1 FILE BIOSIS
L23          0 FILE EMBASE
L24          1 FILE WPIDS
L25          0 FILE JICST-EPLUS
     TOTAL FOR ALL FILES
L26         15 S L19 AND (CANCER OR BREAST CANCER OR TUMOUR OR TUMOR)
L27         14 DUP REM L26 (1 DUPLICATE REMOVED)
L28         73 FILE MEDLINE
L29         45 FILE CAPLUS
L30         87 FILE BIOSIS
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L31           56 FILE EMBASE
L32           17 FILE WPIDS
L33            0 FILE JICST-EPLUS
     TOTAL FOR ALL FILES
L34          278 S ALBERTSON D?/AU,IN
L35          226 FILE MEDLINE
L36          114 FILE CAPLUS
L37          312 FILE BIOSIS
L38          147 FILE EMBASE
L39           23 FILE WPIDS
L40            3 FILE JICST-EPLUS
     TOTAL FOR ALL FILES
L41          825 S PINKEL D?/AU,IN
L42          692 FILE MEDLINE
L43          886 FILE CAPLUS
L44          876 FILE BIOSIS
L45          546 FILE EMBASE
L46          106 FILE WPIDS
L47            9 FILE JICST-EPLUS
     TOTAL FOR ALL FILES
L48         3115 S COLLINS C?/AU,IN
L49         1955 FILE MEDLINE
L50         1671 FILE CAPLUS
L51         2559 FILE BIOSIS
L52         1571 FILE EMBASE
L53          313 FILE WPIDS
L54           21 FILE JICST-EPLUS
     TOTAL FOR ALL FILES
L55         8090 S GRAY J?/AU,IN
L56            2 FILE MEDLINE
L57            6 FILE CAPLUS
L58            5 FILE BIOSIS
L59            3 FILE EMBASE
L60            3 FILE WPIDS
L61            0 FILE JICST-EPLUS
     TOTAL FOR ALL FILES
L62           19 S L55 AND L48 AND L41 AND L34
L63            9 DUP REM L62 (10 DUPLICATES REMOVED)

=> s l19 and amplif?

L64            0 FILE MEDLINE
L65            2 FILE CAPLUS
L66            1 FILE BIOSIS
L67            0 FILE EMBASE
L68            0 FILE WPIDS
L69            0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L70            3 L19 AND AMPLIF?

=> dup rem l70

PROCESSING COMPLETED FOR L70
L71            3 DUP REM L70 (0 DUPLICATES REMOVED)
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L71 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2001 ACS
2000:725793 Document No. 133:291918 **CYP24** gene **amplification** and its use as marker for presence or progression of or predisposition to cancer. Albertson, Donna G.; Pinkel, Daniel; Collins, Colin; Gray, Joe W.; Ystra, Bauke (Regents of the University of California, USA). PCT Int. Appl. WO 2000060109 A1 20001012, 73 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US5972 20000306. PRIORITY: US 1999-285292 19990402.

AB This invention pertains to the discovery that an **amplification** of the **CYP24** gene or an increase in **CYP24** activity is a marker for the presence of, progression of, or predisposition to, a cancer (e.g., breast cancer). Using this information, this invention provides methods of detecting a predisposition to cancer in an animal. The methods involve (i) providing a biol. sample from an animal (e.g. a human patient); (ii) detecting the level of **CYP24** within the biol. sample; and (iii) comparing the level of **CYP24** with a level of **CYP24** in a control sample taken from a normal, cancer-free tissue where an increased level of **CYP24** in the biol. sample compared to the level of **CYP24** in the control sample indicates the presence of said cancer in said animal.

L71 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2001 BIOSIS
2000:388499 Document No.: PREV200000388499. Expression profiling of genes involved in vitamin D metabolism using cDNA microarray technology. Chau, T. (1); Huang, M.; Lai, W. (1); Leung, Y. (1); Wong, M. (1). (1) Department of Applied Biology and Chemical Technology, Hong Kong Polytechnic University, Hong Kong, SAR China. Journal of Bone and Mineral Research, (September, 2000) Vol. 15, No. Suppl. 1, pp. S329. print. Meeting Info.: Twenty-Second Annual Meeting of the American Society for Bone and Mineral Research Toronto, Ontario, Canada September 22-26, 2000 American Society for Bone and Mineral Research. ISSN: 0884-0431.
Language:
English. Summary Language: English.

L71 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2001 ACS
1999:270435 Document No. 131:53709 Liarozole acts synergistically with 1.alpha.,25-dihydroxyvitamin D3 to inhibit growth of DU 145 human prostate cancer cells by blocking 24-hydroxylase activity. Ly, Lan H.; Zhao, Xiao-Yan; Holloway, Leah; Feldman, David (Department of Medicine, Division of Endocrinology, Stanford University School of Medicine, Stanford, CA, 94305, USA). Endocrinology, 140(5), 2071-2076 (English) 1999. CODEN: ENDOAO. ISSN: 0013-7227. Publisher: Endocrine Society.

AB 1.alpha.,25-Dihydroxyvitamin D3 [1,25-(OH)2D3] inhibits the proliferation of many cancer cells in culture, but not the aggressive human prostate cancer cell line DU 145. We postulated that the 1,25-(OH)2D3-resistant phenotype in DU 145 cells might result from the high levels of expression of 25-hydroxyvitamin D-24-hydroxylase (24-hydroxylase) induced by treatment with 1,25-(OH)2D3. As this P 450 enzyme initiates 1,25-(OH)2D3 catabolism, we presumed that a high level of enzyme induction could limit

the effectiveness of the 1,25-(OH)2D3 antiproliferative action. To examine this hypothesis we explored combination therapy with liarozole fumarate (R85,246), an imidazole deriv. currently in trials for prostate cancer therapy. As imidizole derivs. are known to inhibit P 450 enzymes, we postulated that this drug would inhibit 24-hydroxylase activity, increasing the 1,25-(OH)2D3 half-life, thereby enhancing 1,25-(OH)2D3 antiproliferative effects on DU 145 cells. Cell growth was assessed by measurement of viable cells using the MTS assay. When used alone, neither 1,25-(OH)2D3 (1-10 nm) nor liarozole (1-10 .mu.M) inhibited DU 145 cell growth. However, when added together, 1,25-(OH)2D3 (10 nM)/liarozole (1 .mu.M) inhibited growth 65% after 4 days of culture. We used a TLC method to assess 24-hydroxylase activity and demonstrated that liarozole (1-100 .mu.M) inhibited this P 450 enzyme in a dose-dependent manner. Moreover, liarozole treatment caused a significant increase in 1,25-(OH)2D3 half-life from 11 to 31 h. In addn., 1,25-(OH)2D3 can cause homologous up-regulation of the **vitamin D receptor** (**VDR**), and in the presence of liarozole, this effect was **amplified**, thus enhancing 1,25-(OH)2D3 activity. Western blot analyses demonstrated that DU 145 cells treated with 1,25-(OH)2D3/liarozole showed greater **VDR** up-regulation than cells treated with either drug alone. In summary, our data demonstrate that liarozole augments the ability of 1,25-(OH)2D3 to inhibit DU 145 cell growth. The mechanism appears to be due to inhibition of 24-hydroxylase activity, leading to increased 1,25-(OH)2D3 half-life and augmentation of homologous up-regulation of **VDR**. We raise the possibility that combination therapy using 1,25-(OH)2D3 and liarozole or other inhibitors of 24-hydroxylase, both in nontoxic doses, might serve as an effective treatment for prostate cancer.

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